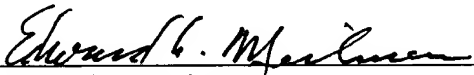




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TRANSMITTAL OF APPEAL BRIEF			Docket No. C2432.0037	
In re Application of: Lars Wiklund et al.				
Application No. 09/773,394-Conf. #5538	Filing Date January 31, 2001	Examiner M. Bahar	Group Art Unit 1617	
Invention: PRESERVATION OF BODILY PROTEIN				
<p style="text-align: center;"><u>TO THE COMMISSIONER OF PATENTS:</u></p> <p>Transmitted herewith is the Appeal Brief in this application, with respect to the Notice of Appeal filed: <u>September 28, 2006</u> .</p> <p>The fee for filing this Appeal Brief <u>\$250.00</u> .</p> <p><input type="checkbox"/> Large Entity <input checked="" type="checkbox"/> Small Entity</p> <p><input type="checkbox"/> A petition for extension of time is also enclosed. The fee for the extension of time is _____ .</p> <p><input type="checkbox"/> A check in the amount of _____ is enclosed.</p> <p><input type="checkbox"/> Charge the amount of the fee to Deposit Account No. <u>50-2215</u> . This sheet is submitted in duplicate.</p> <p><input checked="" type="checkbox"/> Fee has been previously paid. ✓</p> <p><input checked="" type="checkbox"/> The Director is hereby authorized to charge any additional fees that may be required or credit any overpayment to Deposit Account No. <u>50-2215</u> . This sheet is submitted in duplicate.</p> <div style="display: flex; justify-content: space-between; align-items: flex-end;"><div> Edward A. Meilman Attorney Reg. No. : 24,735 DICKSTEIN SHAPIRO LLP 1177 Avenue of the Americas 41st Floor New York, New York 10036-2714 (212) 277-6520</div><div>Dated: <u>November 27, 2006</u></div></div>				



Docket No.: C2432.0037
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:

Lars Wiklund et al.

Application No.: 09/773,394

Confirmation No.: 5538

Filed: January 31, 2001

Art Unit: 1617

For: PRESERVATION OF BODILY PROTEIN

Examiner: M. Bahar

APPEAL BRIEF

MS Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

As required under § 41.37(a), this brief is filed within two months of the Notice of Appeal filed in this case on September 28, 2006, and is in furtherance of said Notice of Appeal.

The fees required under § 41.20(b)(2) are dealt with in the accompanying TRANSMITTAL OF APPEAL BRIEF.

This brief contains items under the following headings as required by 37 C.F.R. § 41.37 and M.P.E.P. § 1206:

- | | |
|------|-----------------------------------|
| I. | Real Party In Interest |
| II | Related Appeals and Interferences |
| III. | Status of Claims |

IV.	Status of Amendments
V.	Summary of Claimed Subject Matter
VI.	Grounds of Rejection to be Reviewed on Appeal
VII.	Argument
VIII.	Claims
Appendix A	Claims
Appendix B	Evidence
Appendix C	Related Proceedings

I. REAL PARTY IN INTEREST

The real party in interest for this appeal is:

Pharmalink AB

II. RELATED APPEALS, INTERFERENCES, AND JUDICIAL PROCEEDINGS

There are no other appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in this appeal.

III. STATUS OF CLAIMS

A. Total Number of Claims in Application

There are 20 claims pending in application.

Current Status of Claims

Claims canceled: 3

Claims withdrawn from consideration but not canceled: 0

Claims pending: 1, 2, and 4-21

Claims allowed: 0

1. Claims rejected: 1, 2, and 4-21

B. Claims On Appeal

The claims on appeal are claims 1, 2, and 4-21

IV. STATUS OF AMENDMENTS

Applicant did not file an Amendment After Final Rejection.

V. SUMMARY OF CLAIMED SUBJECT MATTER

Glutamine, one of the predominant amino acids in the body, is mainly utilized as an energy source and nitrogen carrier. During post-operative and posttraumatic catabolism, its availability is decreased resulting in depletion of skeletal muscle glutamine and, with continued utilization of glutamine by the intestine, to low blood glutamine levels.

The administration of glutamine to a patient in the state of glutamine depletion is less than a direct way of coping with the deficiency since glutamine is poorly soluble in water and cannot be sterilized by autoclavation. A more direct way of preserving or raising blood glutamine levels is highly desirable.

Alpha-ketoglutarate (α -KG), the biologic precursor of glutamine, has been tried in human internal and parental nutrition but in clinical studies, the recorded effect have been small and judged to be of minor importance.

Ammonium has been occasionally administered to patients in the form of a pharmacologically acceptable salt such as a chloride, despite the fact that it is

considered neurotoxin in that high concentrations are known to be neurotoxic. It is known to cause metabolic acidosis. Its recommended pharmaceutical uses are few.

The present invention provides a method of preserving body protein stored in a catabolic patient by the concomitant administration of a pair of pharmaceutical agents in amounts effective to preserve skeletal muscle. The first agent contains alpha-ketoglutarate (α -KG) and/or alpha-ketoglutaric acid (α -KA) and is devoid of ammonium. The second agent contains ammonium but is devoid of alpha-ketoglutarate and alpha-ketoglutaric acid.

A mapping of the independent claims and dependent claims to the extent argued separately includes, but is not limited to, the following:

Independent claim 1 calls for a method of preserving bodily protein stores in a catabolic patient (page 4, lines 20-23), comprising the concomitant (page 4, lines 20-23) and separate (page 12, lines 12-16) administration of a pair of pharmaceutical agents consisting essentially of (a) a first composition containing at least one of α -ketoglutarate and α -ketoglutaric acid and being devoid of ammonium (page 4, lines 20-23; page 12, lines 10-16) and (b) a second composition containing ammonium and being devoid of a α -ketoglutarate and α -ketoglutaric acid (page 4, lines 20-23; page 12, lines 10-16), the amounts of the pair being effective to preserve skeletal muscle (page 4, lines 20-23), wherein any composition administered containing at least one of α -ketoglutarate and α -ketoglutaric acid is devoid of ammonium (page 12, lines 12-16).

Independent claim 15 calls for a pharmaceutical dosage unit comprising a first and second separate pharmaceutical compositions (page 4, lines 20-23; page 12, lines 10-16), the first composition comprising at least one of α -ketoglutarate and α -ketoglutaric acid in a pharmaceutically acceptable carrier and being devoid of ammonium (page 4, lines 20-23; page 12, lines 10-16), and the second pharmaceutical

composition comprising ammonium in a pharmaceutically acceptable carrier and being 16), the total amount of the at least one of α -ketoglutarate and α -ketoglutaric acid and the ammonium being effective to preserve skeletal muscle (page 4, lines 20-23), and wherein the amount administered of said at least one of α -ketoglutarate and α -ketoglutaric acid is from $0.02 \mu\text{mol}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ to $30 \mu\text{mol}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ (original claim 7) and the amount of infusion administered of NH_4^+ is from $0.5 \mu\text{mol}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ to $20 \mu\text{mol}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ (original claim 9).

Claim 6 specifies that the administrations are by infusion (page 12, lines 10-16) while claims 7-10 and 15-19 specify rates of infusion (page 5, lines 12-16).

Claims 11 - 14 recite that the infusion of the ammonium is increased over the period of administration (page 5, lines 14-16).

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

All claims are rejected under 35 U.S.C. § 112, first paragraph as failing to comply with the written description requirement.

All claims are rejected under 35 U.S.C. § 112, second paragraph as being indefinite.

All claims are rejected under 35 U.S.C. § 103(a) over Veech (U.S. 5,719,119), Vinnars (U.S. 5,310,768), Taconic (www.taconic.com/anmodels/spragued.htm) and Bollish (U.S. 5,219,330).

VII. ARGUMENT

1. Introduction

On August 30, 2005, the Board remanded the appeal of this case to the Examiner because the Examiner had not properly interpreted the pending claims. Since that time, the claims have been amended to address the issues raised by the Board. For example, the Board observed that the claim required concomitant administrative of two pharmaceutical agents but did not appear to require the administrative of two separate compositions. The claims were amended to call for the concomitant administration of two separate compositions but the Examiner now asserts that change renders the claims indefinite.

The Board's remand also focused on the open term "comprising" as possibly being sufficiently broadening so that the claims could read on an α -KA/ α -HG composition possibly containing ammonia and the ammonium compositions possibly containing α -KA or α -KG. The claims were amended to avoid this possibility but the Examiner asserts in this Appeal that there is no basis in the application for such compositions.

**2. The claims comply with the written description
requirement of 35 U.S.C. 112, first paragraph**

The Final Rejection contends that the claims fail to comply with the first paragraph of 35 U.S.C. 112 because the application as originally filed lacks support for separate compositions containing α -KA/ α -KG and ammonia, respectively, that each composition is devoid of the other agent, that the application lacks support for "separate" administration and claim 15 lacks support for the compositions being "a first and second" separate pharmaceutical compositions.

These assertions make no sense. For instance, to object to calling the compositions "first" and "second" in order to differentiate them exalts form over

substance and seems to demand support in the application *in hac verba* even though neither the statute nor the case law requires such exactitude.

In the experimental protocol, the animals of Group 1 received an infusion of ammonium chloride in saline and a second infusion of α -KG in saline. This is described on page 12 of the application. Clearly the α -KG composition was devoid of ammonium and the ammonium composition was devoid of the α -KG. This description fully supports the claims and is sufficient to satisfy the written description requirement.

3. The claims are not indefinite in violation of 35 U.S.C. 112, 2nd paragraph

This rejection is based on the phrase “concomitant and separate” administration being “confusing” (Final Rejection page 4). But both of these words “concomitant” and “separate” are being used in their normal everyday sense. Concomitant means to accompany. Separate means the two compositions are not present in a single composition. Accordingly, the phrase “concomitant and separate” means that two compositions (rather than a mixture) are administered at about the same time. The phrase, and the claims, are not indefinite.

4. The Combination Of Veech, Vinnars, Taconic And Bollish

Does Not Render The Claims Obvious Under 35 U.S.C. § 103

One of the predominant amino acids in the body, glutamine, is mainly utilized as an energy source and nitrogen carrier. Its availability is decreased during post-operative and posttraumatic catabolism, resulting in depletion of skeletal muscle glutamine and, with continued utilization of glutamine by the intestine, to low blood

glutamine levels. While administration of glutamine to a patient in the state of glutamine depletion would appear to be desirable, it is less than a direct way of coping with the deficiency since glutamine is poorly soluble in water and cannot be sterilized by autoclavation. See, e.g., Vinnars at column 2, lines 30-40. A more direct way of preserving or raising blood glutamine levels is highly desirable.

The present invention provides a method of preserving body protein stored in a catabolic patient by the concomitant administration of a pair of pharmaceutical agents in amounts effective to preserve skeletal muscle. The first agent contains alpha-ketoglutarate (α -KG) and/or alpha-ketoglutaric acid (α -KA) and is devoid of ammonium. The second agent contains ammonium but is devoid of alpha-ketoglutarate and alpha-ketoglutaric acid. A pharmaceutical dosage unit containing these separate compositions is also claimed.

Alpha-ketoglutarate (α -KG) is a biologic precursor of glutamine. Its use has been investigated in human internal and parental nutrition but in clinical studies, the recorded effects have been small and judged to be of minor importance. As noted *infra*, a recent study concludes there is no valid rationale for its use in an enteral composition.

Ammonium has been occasionally administered to patients in the form of a pharmacologically acceptable salt such as a chloride, despite the fact that it is considered a neurotoxin because high concentrations are known to be neurotoxic. It causes metabolic acidosis. The recommended pharmaceutical uses of ammonium are few.

Nevertheless, the inventors found out that concomitant administration was advantageous. In another surprising finding, the inventors also found that infusion increased arterial glutamine concentration in a dose dependent fashion when the ammonium load was increased and the dose of α -KG was kept constant but not when

the α -KG load was increased and the dose of ammonium was kept constant. Data establishing this surprising finding is presented in the application.

The primary reference relied on by the Examiner, Veech, relates to a parenteral nutritional aqueous solution which contains one or more of 20 metabolizable nitrogen containing compounds, one or more of 6 carboxylic metabolite anions and one or more of 5 cations. Among the 6 carboxylic metabolite anions is alpha-ketoglutarate and among the 5 cations is ammonium. The patent sets forth reasons for each of these materials to be present. It teaches (col. 13, lines 62-65) that the presence of the metabolite anions in the composition of the Veech invention exert a desirable alkalinizing action which avoids metabolic acidosis. The patent also points out that normal plasma contains concentrations of ammonium, α -KG and glutamate which is equivalent to the free mitochondrial NAD/NADH ratio and if fluids are given which do not contain these substances, the cells alter their metabolism to realize that ratio. Accordingly, the presence of both α -KG and ammonium in the amino acid solution containing glutamate controls the redox state of the mitochondria (col.13, line 66 to col. 14, line 20). Also, the presence of both ketoglutarate/glutamine at concentrations around the physiologically normal avoids the use of free ammonia, but generates ammonia and the production of intracellular glutamate (col. 14, lines 21-24). Thus, the reference teaches the presence of both ammonium and α -KG in the same solution in order to control the redox state. Col. 13, line 66 et. seq. Further, the presence of both is designed to make the solution electrically neutral. (Col. 18, lines 51 et. seq.).

If the metabolite anion α -KG is present in the composition of the Veech for the purpose of avoiding metabolic acidosis, why would one employ a separate administration of a material such as ammonium which is known to cause metabolic acidosis when so administered? There is no reason.

If the absence of ammonium or α -KG in a single fluid causes cells to alter their metabolism, why would one intentionally omit one? There is no reason.

If the presence of both α -KG and ammonium in the amino acid solution containing glutamate controls the redox state of the mitochondria, why would one be omitted? There is no reason.

If Veech teaches his combination avoids the use of free ammonia, why would one administer ammonium separately? There is no reason.

It will be appreciated from the foregoing, that the Veech reference teaches solution which contains a combination of alpha-ketoglutarate and ammonium in all instances and further provides reasons why both should be present. There is no reason or motivation to separate them.

Vinnars teaches the addition of alpha-ketoglutarate to a conventional amino acid solution but does not mention ammonium. Since this teaching is also found in Veech, the Vinnars reference does not add anything of substance vis-à-vis the instant rejection. Apparently, the only additional disclosure in this reference on which reliance is being had is the fact that the concentration administered of the alpha-ketoglutarate should be at least 0.1 g/kg body weight/day.

Vinnars points out that that glutamine reduction was not affected by enteral or parenteral nutritional support before the invention there described. He found that alpha-ketoglutarate worked in certain compositions even though ornithine-alpha-ketoglutarate had a limited effect and it was not known whether there would be any clinical advantage (column 2, lines 11-20). A recent paper by Wiren (copy in Appendix B) describes a study to evaluate the feasibility of using α -ketoglutarate enrichment in enteral feeding and the effect on protein metabolism after major surgery. The authors

concluded that enrichment of a whole protein-based formula with α -ketoglutarate did not improve protein metabolism or decrease muscle catabolism after major abdominal surgery. See e.g., the summary on page 725 and the concluding paragraph in the paper. The findings of the study were sufficiently important to elicit an editorial opinion (also in Appendix B). Note that the concluding sentence by Dr. Cynober in that opinion states that based on both the Wiren study and the available literature, there is no rationale for providing an α -ketoglutarate enriched enteral diet in post-operative patients. These teachings indicate that predictability in this art is limited.

The combination of Veech and Vinnars advanced in this rejection does not teach or suggest the use of two separate compositions, one containing alpha-ketoglutarate and/or alpha-ketoglutaric acid and the other containing ammonia, when neither of these compositions contain the other substance. The Veech reference discloses them but calls for a single solution containing both α -KG and ammonium, provides reasons both should be present and does not suggest separating them. The other references do not provide the missing suggestion.

The Examiner has sought to overcome this basic deficiency by asserting that one skilled in the art would have been motivated to separate the two materials. The reason given is that both are known to be useful in methods of treating post-operative/post-traumatic patients and normalizing/preserving skeletal muscle glutamine/nitrogen content. This attempted hindsight justification should be rejected for at least two reasons. First, there is no factual basis for the assertion that ammonium alone is known to be useful in such methods. The rejection does not identify where such disclosure is found nor has any such teaching been found in the references applied or elsewhere in the instant record. Veech does teach the use of ammonium but only within the same aqueous solution as the α -ketoglutarate and there is no implication it can be used separately. Quite the contrary, Veech provides a variety of reasons why the

ammonium should be in the same composition as the α -KG and this is a second reason for rejecting the alleged motivation. If the presence of a material in a composition has been taught to provide advantages, then there must be a good reason existent before one skilled in the art would separate that material from the composition. The rejection does not even hypothesize such a reason.

In the case of *In re Freed*, 165 USPQ 570 (1970), the CCPA had occasion to observe that “. . . it seems more logical and reasonable to infer that one teaching a chemical reaction process would set out the least number of reactions thought to be necessary to accomplish the desired objectives.” Applying similar logic, it seems more logical that one teaching a composition would want all of the components in a single composition so that the least number of compositions need be administered. Separating the components in the absence of a reason to do so is illogical.

The Examiner also attempts to provide motivation by asserting that administering two agents is an obvious alternative to administering a mixture. Once again, it is respectfully submitted that one would not separate α -KG and ammonium in the absence of a reason and no reason has even been hypothesized.

Taconic has apparently been cited only to show the “normal” weight of certain male rats. Bollish was cited to show that certain administration rates are within the realm of possibility. Neither teaching cures the basic deficiencies in the rejection.

The foregoing discussion has focused on the independent claims. There are additional reasons why groups of the dependent claims are patentable over this art.

Claims 2-4 and 21 recite the duration of administration. Claim 20 (on which claim 21 is dependent) specifies that ammonium chloride is administered. There is no basis in the art to contend these claims are obvious.

Claim 6 specifies that the administrations are by infusion. Claim 7-10 and 15-19 specify rates of infusion. Beyond the fact that the references do not teach or suggest two separate infusions, there is no factual basis for selecting any rate of infusion. The Examiner attempts to overcome this deficiency by citing Bollish and asserting that the determination of amounts is mere optimization. Bollish merely shows that certain rates are within the realm of possibility. Accordingly, the assertion is merely a suggestion that it would be obvious to try various administration rates and find one which works, i.e., it is obvious to try various rates. It is well established that an obvious to try standard does not meet the requirements of §103.

Claims 11 - 14 recite that the infusion of the ammonium is increased over the period of administration. The art does not suggest changing the rate of administration of any material during the administration period for any reason. As noted earlier, changing the ammonium rate provides advantages which are not realized when the rate of the α -KG is increased. Nothing in the art suggests the ammonium rate should be changed.

For all the reasons set forth above, it is respectfully submitted that the rejection under §103 should be reversed.

5. Conclusion

For the reasons stated above, the Final Rejection should be reversed.

VIII. CLAIMS

A copy of the claims involved in the present appeal is attached hereto as Appendix A.

Dated:

Respectfully submitted,

By Edward A. Meilman

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APPENDIX A

Claims Involved in the Appeal of Application Serial No. 09/773,394

1. A method of preserving bodily protein stores in a catabolic patient, comprising the concomitant and separate administration of a pair of pharmaceutical agents consisting essentially of (a) a first composition containing at least one of α -ketoglutarate and α -ketoglutaric acid and being devoid of ammonium, and (b) a second composition containing ammonium and being devoid of a α -ketoglutarate and α -ketoglutaric acid, the amounts of the pair being effective to preserve skeletal muscle, wherein any composition administered containing at least one of α -ketoglutarate and α -ketoglutaric acid is devoid of ammonium.
2. The method of claim 1, wherein the administration of (a) or (b) or both lasts for more than one hour.
4. The method of claim 2, wherein the concomitant administration lasts for more than 6 hours but less than 36 hours.
5. The method of claim 1, wherein the administration is to a patient having undergone trauma or surgery and the administration is intermittent or continuous for at least three days of the posttraumatic/postoperative period during which the patient is in a catabolic state.
6. The method of claim 1, wherein administration is by infusion.
7. The method of claim 6, wherein the amount of infusion administered of

(a) is from $0.02 \text{ mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ to $30 \text{ mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$.

8. The method of claim 7, wherein the amount of infusion administered of (a) is from $0.5 \text{ mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ to $15 \text{ mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$.

9. The method of claim 6, wherein the amount of infusion administered of NH_4^+ is from $0.5 \text{ mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ to $20 \text{ mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$.

10. The method of claim 9, wherein the amount of infusion administered of NH_4^+ is from $1 \text{ mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ to $10 \text{ mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$.

11. The method of claim 9, wherein the amount of infusion administered of NH_4^+ is increased over the period of administration.

12. The method of claim 11, wherein the amount of infusion administered of (a) is from $0.02 \text{ mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ to $30 \text{ mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$.

13. The method of claim 11, wherein said increase is by a factor of from 1.5 to 8.

14. The method of claim 13, wherein said increase is by a factor of from 2 to 5.

15. A pharmaceutical dosage unit comprising a first and second separate pharmaceutical compositions, the first composition comprising at least one of α -ketoglutarate and α -ketoglutaric acid in a pharmaceutically acceptable carrier and being devoid of ammonium, and the second pharmaceutical composition comprising ammonium in a pharmaceutically acceptable carrier and being devoid of α -

ketoglutarate and α -ketoglutaric acid, the total amount of the at least one of α -ketoglutarate and α -ketoglutaric acid and the ammonium being effective to preserve skeletal muscle, and wherein the amount administered of said at least one of α -ketoglutarate and α -ketoglutaric acid is from 0.02 1mol,kg⁻¹,min⁻¹ to 30 1mol,kg⁻¹,min⁻¹ and the amount of infusion administered of NH₄⁺ is from 0.5 1mol,kg⁻¹,min⁻¹ to 20 1mol,kg⁻¹,min⁻¹.

16. The unit of claim 15, wherein both carriers are an infusion carrier.
17. The unit of claim 15, wherein both carriers are an oral carrier.
18. The unit of claim 15, wherein the α -ketoglutarate is in form of its sodium.
19. The unit of claim 15, wherein ammonium is in form of its chloride.
20. The method of 1, wherein the ammonium is ammonium chloride.
21. The method of claim 20, wherein the administration of (a) or (b) or both lasts for more than one hour.

APPENDIX B

The following evidence was entered by the Examiner:

Wiren et al., α -Ketogutarate-Supplemented Enteral Nutrition: Effects on Postoperative Nitrogen Balance and Muscle Catabolism, Nutrition 18:725-728, 2002

Cynober, Goodbye Sodium α -Ketoglutarate, Nutrition 18:772, 2002

Goodbye Sodium α -Ketoglutarate?

In this issue of *Nutrition*, Wirén and associates¹ report convincing results indicating that a whole-protein-based formula for enteral nutrition supplemented with sodium α -ketoglutarate (α KG) neither affects protein metabolism nor decreases muscle catabolism after major abdominal surgery, compared with a standard isocaloric isonitrogenous formula. This soundly designed work, involving isonitrogenous and isocaloric intake in homogeneous groups of patients, raises a number of questions.

WHAT IS THE RATIONALE FOR SUPPLEMENTATION OF AN ENTERAL DIET WITH SODIUM α KG? Wirén and associates state that α KG may be used directly as an energy source in the intestinal mucosa. This is true because α KG is taken up by enterocytes,² as it is by other cells.³ They also claim that α KG can be converted to glutamine (GLN) in the mucosa or can decrease gut consumption of GLN, thereby exerting a sparing effect on endogenous GLN pools. I have some doubts about these hypotheses. First, enterocytes are primarily GLN consumers⁴ expressing high glutaminase activity and low (if any) GLN synthase activity. Second, we have repeatedly demonstrated⁵ in animal models that α KG does not exhibit any sparing effect on endogenous GLN pools. This clearly distinguishes sodium α KG from α KG combined with ornithine (ornithine α -ketoglutarate, or OKG), as discussed below.

WHY α KG AND NOT GLN OR EVEN GLUTAMATE? Considering the potential physiologic and pharmacologic regulating actions of GLN,⁶ it makes sense to supply compounds able to maintain homeostasis of this amino acid. The simplest way is to provide GLN itself. However, provision of GLN by the enteral route does not seem very efficient in improving nutrition status,^{7,8} despite what has been repeatedly demonstrated when GLN is supplied by the parenteral route, in free form or as a dipeptide.^{6,9} There are at least two reasons for this discrepancy:

1. Most of the GLN given by the enteral route is metabolized in the splanchnic bed, and in these conditions GLN has little chance of appearing in the peripheral circulation and, hence, modulating muscle protein metabolism. It seems that an intake of more than 30 g/d of GLN is required to saturate splanchnic extraction.¹⁰ Notably, patients in the study by Wirén et al. received 8 g/d of α KG. At this dosage, it is unlikely that much (if any) α KG escapes the splanchnic bed. We gave 3.6 g sodium α KG to healthy subjects (in one bolus by the oral route) and did not detect any variation in plasma α KG levels.¹¹
2. It seems that GLN taken up by the vascular side of enterocytes is channeled differently from that taken up at the luminal side. Only the former may be directed toward pathways regulating trophic processes, whereas the latter is used mainly for energy expenditure.

Another limitation in free GLN use is its instability in solution. However, sodium α KG is not very stable in solution¹² and is very acidic, which may compromise the stability of the polymeric formula.

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Why not use glutamate (GLU)? GLU has a bad reputation because of its association with the so-called Chinese restaurant syndrome. Also, studies have indicated that exogenous GLU does not mix with the GLU pool, which is the precursor for GLN synthesis.¹³ However, there are convincing results^{14,15} indicating that a GLU-enriched diet may increase GLN pools, probably by sparing the use of GLN in enterocytes.

Therefore, the rationale for providing sodium α KG, rather than GLN or GLU, in enteral nutrition is weak.

TO BE KEPT IN MIND: α KG DOES NOT REPRODUCE OKG EFFECTS. Throughout their paper, Wirén and coworkers underline the actions of OKG on protein metabolism. In my opinion, they do not sufficiently emphasize that OKG is different from sodium α KG, a fact that is also insufficiently recognized by other experts in the field.⁹ OKG action results from the interaction between α KG and ornithine,^{5,16} and α KG (unlike OKG) neither affects insulin secretion¹¹ nor has any metabolic (unfortunately amino acid plasma levels were not measured by Wirén et al.) or regulatory effects when supplied by the oral or enteral route. Finally, OKG is stable in solution and has a neutral pH over a wide range of concentrations.¹⁷ Therefore, OKG is a potent immunopharmacological nutrient, whereas sodium α KG likely is not.

OTHER CONSIDERATIONS AND CONCLUSION. As rightly stated by Wirén et al., the fact that it was not possible to reach the nutritional goal during the first 5 d after surgery (actual nitrogen intake: 0.10 g/d) could obscure possible effects of the α KG enrichment. It certainly makes sense that pharmacological nutrients can promote net protein synthesis, provided a sufficient amount of nitrogen is absorbed. Also, GLN and OKG are effective in correcting protein metabolic disturbances only in cases where such disturbances exist. When patients are not catabolic, GLN supplementation has no effect.¹⁸ This may be the case in the present study, where patients exhibited only moderate negative nitrogen balance and moderate increases in 3-methylhistidine excretion.

Overall, on the basis of the results of this study and the available literature, there is no rationale for providing an α KG-enriched enteral diet in postoperative patients.

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Amino Acids: Fuel, Building Blocks for Proteins, and Signals

INTRODUCTION

Amino acid physiology is a field of particular complexity because of the number of amino acids and their multiple specific functions.¹ Based on present knowledge, it is not possible to completely describe their individual kinetics and metabolic actions and simultaneously depict their interaction in regulating protein synthesis. As a consequence, the interpretation of plasma amino acid profiles in pathologic conditions is more phenomenonic than mechanistic, and the choice of the optimal amino acid mix supplementation for therapeutic purposes is based largely on empiric criteria. In this issue of *Nutrition*, Dr. Cynober describes the state of the art for using amino acid concentrations as a valuable tool in the clinical setting. He correctly points out that plasma concentrations do not necessarily reflect fluxes, the most appropriate parameters to supply over time the correct amount of a given amino acid. Serial plasma amino acid measurements in response to a dynamic test (the enteral supplementation) might improve our insight into amino acid requirements. It is generally felt that formulating the correct balance of an amino acid solution for enteral infusion is the key to meet the requirements in specific clinical situations. The latter objective, to exactly match each amino acid requirement with its supplementation, is logical and extremely important to prevent the potentially harmful effects of amino acid overfeeding or under-replacement. Present knowledge, however, suggests that some amino acids (e.g., glutamine, arginine, and branched-chain forms) could be used as drugs to promote some desirable effects such as protein anabolism, immunotrophism, or nitric oxide generation. Amino acid supplementation "beyond their requirements" would significantly change this approach; even though it is not presently possible to devise clear clinical procedures for this approach, this

perspective should be kept in mind, and amino acid physiology and pathophysiology should be interpreted in this light.

A comprehensive view of amino acid physiology, pathophysiology, and their potential clinical use should take into account at least three interpretative levels: fuel, building blocks for proteins, and signals. Amino acids as fuel have been perceived somewhat in contrast with amino acids as building blocks for proteins. The diversion of amino acid flux from oxidation into protein incorporation to preserve protein mass may be desirable because protein depletion greater than 25% leads to death. Nonetheless, amino acids are an important fuel for several tissues: postabsorptively, their oxidation supports 15% of the resting energy expenditure. During exercise, muscle amino acids may produce significant amounts of energy via oxidative deamination of aspartate to provide ammonia for the synthesis of AMP from IMP and intermediates for the citric acid cycle. Among the amino acids readily converted to aspartate, there are glutamine and glutamate, the most abundant amino acids in the body, especially concentrated in the muscle. During feeding, the splanchnic bed extracts and immediately oxidizes a large amount of the enteral non-essential amino acids, including the totality of glutamate and the majority of glutamine and alanine. Glutamine in turn is an important fuel for the intestine and the immune system, and its depletion is synonymous with organ dysfunction. Glutamine is a "conditionally essential" amino acid because, in certain conditions, glutamine de novo synthesis is not sufficient to meet its endogenous requirements.² These lines of evidence support the idea that amino acid supplementation for oxidation is important, especially when the requirements increase during pathologic processes.

Amino acids as precursors for protein anabolism is the second important level at which amino acid metabolism should be considered. It is well known that the limitation in single amino acid availability limits the entire protein synthetic rate. The diversion of specific amino acids into oxidation may imbalance the free pool available for protein synthesis. The imbalance in turn may reduce protein synthesis. For this reason, it is necessary that, for each clinical condition, the amino acid requirements for oxidation are completely understood and correctly met by amino acid supplementation. However, a balanced pool of amino acids for protein synthesis is necessary but insufficient to promote protein anabolism. Amino acid administration increases protein synthesis in healthy humans, but clinical experience shows that amino acid overfeeding in the critically ill patient simply increases amino acid oxidation and not protein synthesis. This frustrating event during catabolic illness reflects an adverse hormonal and cytokine milieu that increases proteolysis and accelerates the use of specific amino acids. Among the factors, cortisol is a major protein catabolic hormone that also increases the glutamine flux.³ A prominent feature of the protein catabolic mode in critically ill patients is the resistance to the metabolic actions of insulin. The cellular bases for the regulation of protein synthesis have been recently elucidated. Several kinases (p70S6 kinase, mitogen-activated protein kinases, and PHAS-1) affect ribosomal activity and are regulated in a complex fashion by upstream mediators depending on hormone signals.⁴ The signals resulting from the insulin interaction with its own receptor and leading to protein anabolism are subject to modulation by catabolic hormones such as cortisol and by inflammatory cytokines such as tumor necrosis factor- α . In addition to amino acid precursor availability, intracellular signaling is important to regulate protein anabolism, and its modulation should be taken into account in nutritional strategies.

Interestingly, the intracellular signaling pathways that were initially described in terms of hormone-responsive transduction elements also respond to nutrient stimuli. It is now clear that amino acids are such modulators.^{5,6} In various mammalian tissues including the myocardium, the skeletal muscle, and the liver, amino acids (branched chain) activate p70S6 kinase and PHAS-1.⁷⁻⁹ Such important modulators of protein synthesis are affected in a complex fashion and at various levels with insulinlike and insulin

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α -Ketoglutarate—Supplemented Enteral Nutrition: Effects on Postoperative Nitrogen Balance and Muscle Catabolism

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OBJECTIVE: Enteral feeding in the early postoperative phase may improve gut integrity and reduce infectious complications after trauma and surgery. The aim of the current study was to evaluate the feasibility of α -ketoglutarate enrichment of enteral feeding and the effect on protein metabolism after major surgery.

METHODS: Patients undergoing elective abdominal surgery were randomly allocated to receive a standard whole-protein-based enteral nutrition solution ($n = 9$) or an isonitrogenous, isocaloric solution enriched with α -ketoglutarate ($n = 11$) for 5 d postoperatively. The nutritional goals by day 4 were 25 kcal and 0.17 g of nitrogen, respectively, per kilogram of body weight every 24 h. Standard blood analysis, including prealbumin and C-peptide, was performed preoperatively and on days 1, 3, and 6. Urine was collected daily for nitrogen and 3-methylhistidine analyses.

RESULTS: Due to restricted tolerance to enteral feeding, the nitrogen delivery reached only 0.10 g of nitrogen per kilogram of body weight. Transthyretin decreased by 25% in both groups, and albumin decreased significantly in the enriched group compared with the standard nutrition. There were no significant differences in nitrogen balance, excretion of 3-methylhistidine, or clinical outcome between groups.

CONCLUSIONS: Enrichment of a whole-protein-based formula with α -ketoglutarate did not improve protein metabolism or decrease muscle catabolism after major abdominal surgery. *Nutrition* 2002;18:725–728. ©Elsevier Science Inc. 2002

KEY WORDS: enteral nutrition, α -ketoglutarate, nitrogen balance, muscle catabolism, surgery

INTRODUCTION

Early enteral feeding may be beneficial to gut integrity. The reduction of infectious complications after trauma and surgery seen with enteral feeding is thought to be due to the trophic effects of intraluminal nutrients on the intestinal mucosa and the gut-associated lymphatic tissue.^{1–4} Specific nutrients such as glutamine and arginine also have been reported to reduce infectious complications after trauma and major abdominal surgery.^{5–7}

α -Ketoglutarate (AKG) has been suggested to be a gut nutrient and potentially a muscle catabolism-reducing agent when provided parenterally. In a series of animal experiments, glutamine improved intestinal mucosal structure and function and reduced bacterial translocation, degree of sepsis, and mortality.⁶ Enteral glutamine supplementation improved outcome after stays in the intensive care unit.^{7,8} Glutamine is present in most protein-based enteral formulas, but one of the clinical problems in postoperative enteral feeding is the difficulty in attaining the volumes needed to cover protein requirements. Supplementation with gut-specific nutrients might increase the efficacy of enteral nutrition.

AKG is the precursor to glutamate and glutamine and is a central part of the tricarboxylic cycle. Adding AKG to total parenteral nutrition preparations prevented the early decrease in skeletal muscle glutamine that is usually seen after surgery.⁹ When AKG was given parenterally with a glucose solution, it prevented a decrease in plasma glutamate and muscle glutamine 24 h after elective hip replacement surgery.¹⁰

Enterally administered AKG can be used directly as an energy resource in the intestinal mucosa without increasing the nitrogen load or it can be converted into glutamine in the mucosa. In a human study, most enterally administered AKG was metabolized directly in the intestinal mucosa.¹¹ In burned rats, AKG in combination with ornithine or arginine significantly increased plasma and muscle glutamine concentrations compared with glycine.¹² We hypothesized that supplementing enteral nutrition with a glutamine precursor would decrease gut consumption of glutamine and would have indirect but positive effects on nitrogen metabolism and skeletal muscle catabolism.

The aim of this pilot study was to compare protein metabolism, nitrogen balance, muscle catabolism, and clinical outcome in patients given enteral feeding supplemented with AKG or an isonitrogenous, isocaloric standard enteral nutrition after major elective abdominal surgery.

MATERIALS AND METHODS

Patients aged 18 to 80 y who were admitted for elective major gastrointestinal surgery and were expected to need at least 5 d of

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TABLE I.

DEMOGRAPHICS, OPERATIVE PROCEDURE, AND DIAGNOSES*		
	Standard (n = 9)	Enriched (n = 11)
Male/female	8/1	7/4
Age (y)	55.2 (15)	55.9 (17)
Weight (kg)	77.8 (10)	75.2 (14)
BMI (kg/m ²)	24	24
SGA (A/B/C)	7/1/1	6/5/0
Operating time (min)	220 (114)	321 (230)
Blood loss (mL)	677 (636)	833 (634)
Gastric cancer	1	3
GI malignancies	3	1
Benign gastric disease	1	2
GERD	1	2
Esophageal, benign	0	2
Colorectal, benign	1	0
Benign GI disease	2	1
Malignant/benign (8/12)	4/5	4/7

* Data are presented as mean (standard deviation). BMI, body mass index; GI, gastrointestinal; SGA, Subjective Global Assessment.

postoperative rehydration were eligible to enter the study. Patients were excluded from the study if they had one or more of the following conditions: a body weight below 50 or over 100 kg, weight reduction greater than 15% in the previous 3 mo, corticosteroid treatment during the previous 3 mo, soy protein allergy, intestinal dysmotility, carcinosis, current cytotoxic treatment, insulin-dependent diabetes mellitus, cardiac insufficiency, renal disease with serum creatinine levels above 175 μ M/L, liver disease with serum bilirubin levels greater than 50 μ M/L, septic states, an ileostomy, planned surgery for a small intestinal resection longer than 50 cm, or planned creation of an ileostomy.

Informed oral consent was obtained from all patients before the start of the study. Twenty-two patients were randomly allocated to receive enteral nutrition supplemented with AKG or standard enteral nutrition for 5 d postoperatively. Two patients were withdrawn from the control group due to dislocation of the nasojejunal catheter and unwillingness to continue participation after surgery. Twenty patients completed the study protocol. The protocol of the study was approved by the Ethical Committee of University Hospital in Linköping, Sweden.

Table I summarizes the demographics, diagnosis, and operative trauma of the patients. A nutritional assessment was made preoperatively including indirect calorimetry, bioelectrical impedance analysis, a functional evaluation according to the Subjective Global Assessment, and an estimate of weight loss during the previous 3 mo, and measurements of serum albumin (g/L) and serum transthyretin (prealbumin; g/L). Patients received increasing volumes of fluid and nutrition beginning on postoperative day 1, and the goal was 25 kcal and 0.17 g of nitrogen per kilogram of body weight in a total volume of 30 mL/kg of body weight by day 4. Equal amounts of parenteral glucose were given to both groups during the first 3 d, and non-caloric fluid substitution was given as needed. Enteral administration was started the first day after surgery through a needle catheter jejunostomy or a gastrojejunostomy placed at surgery. The enteral solutions were isonitrogenous and isocaloric whole-protein-based formulas with or without AKG supplementation (Table II). The starting rate of 50 mL/h was gradually increased to 150 to 200 mL/h with a pump device. Gastrointestinal signs and symptoms were recorded daily, and the jejunal infusion rate was reduced or discontinued if the patient complained of belching, abdominal cramps, or nausea. If the infusion was discontinued, it was resumed at a lower rate 2 h later.

TABLE II.

CONTENT 100 ML OF ENTERAL SOLUTION		
	Enriched	Standard
Protein (g)	5.1	4.9
Nitrogen (g)	0.8	0.8
Fat (g)	4.5	4.3
Carbohydrate (g)	14.6	15.8
Lactose (g)	0.32	0.32
Energy (kJ/kcal)	501/119	511/123
α -Ketoglutarate (g)	0.79	
Sodium (mg)	225	129
Potassium (mg)	280	161
Magnesium (mg)	24.7	24.7
Calcium (mg)	92.4	81.8
Phosphorus (mg)	61.3	64.5
Copper (mg)	0.14	0.15
Zinc (mg)	1.18	1.2
Manganese (mg)	0.40	0.40
Iron (mg)	1.51	1.40
Chloride (mg)	161	172
Vitamin A (mg)	0.067	0.068
Vitamin D (mg)	0.43	0.43
Vitamin E (mg)	2.7	2.6
Vitamin K1 (mg)	10.1	9.9
Vitamin B1 (mg)	0.19	0.19
Vitamin B2 (mg)	0.16	0.15
Niacin (mg)	1.4	1.5
Vitamin B6 (mg)	0.16	0.14
Vitamin B12 (mg)	1.61	1.5
Pantothenic acid (mg)	1.02	0.91
Biotin (mg)	24.7	23.7
Folic acid (mg)	43	30.1
Vitamin C (mg)	20.4	19.4
Cholin (mg)	26.9	24.7
Inositol (mg)	37.6	36.6
Density	1075	1076
pH	7.13	7.47
Osmolality	487	372

Patients were allowed free intake of non-caloric fluid and usually started this intake by day 3. Each patient's temperature, blood pressure, heart rate, complications, and subjective evaluation of quality of life were noted daily, and the clinical course was recorded. Blood samples were taken preoperatively after an overnight fast and during the study period on days 1, 3, and 6 for standard analysis including C-peptide and transthyretin. Urine was collected daily for nitrogen and 3-methylhistidine analyses.

Nitrogen excretion was determined by the Kjeldahl method, and nitrogen balance was calculated by using 30 mg·kg⁻¹·d⁻¹ as an estimate of the nitrogen losses by the skin and stool. Myofibrillar protein degradation was evaluated by measurement of urinary 3-methylhistidine with the use of a conventional amino-acid analyzer (Beckman System 6300, Beckman Instruments, Palo Alto, CA, USA).

Data are presented as mean (standard error). Group comparisons were made with analysis of variance and *t* test for paired observations. *P* < 0.05 was considered significant.

RESULTS

The study groups were comparable in sex distribution, age, body weight, underlying diseases, and the proportion of patients with malignant and benign disease (Table I). Operating time and blood loss did not differ significantly between groups.

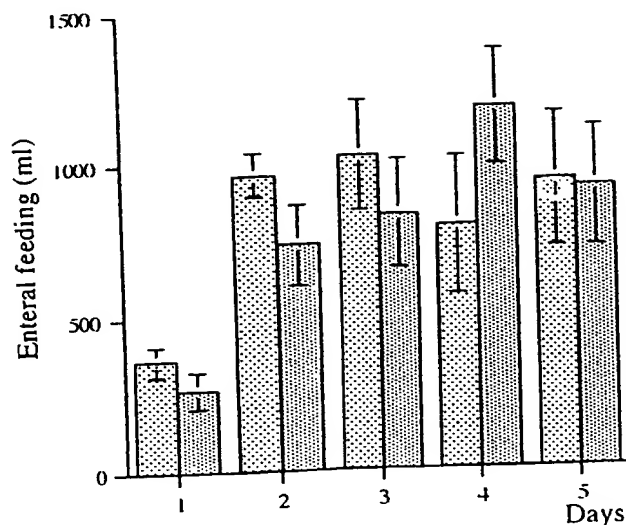


FIG. 1. Mean (standard error) volumes (mL/24 h) of enteral feeding during postoperative days 1 to 5 after major abdominal surgery. Dotted bars indicate standard nutrition, and solid bars indicate AKG-supplemented nutrition. There were no significant differences between groups. AKG, α -ketoglutarate.

Because nausea, vomiting, and abdominal pain limited patients' tolerance for enteral nutrition of 3 to 4 d postoperatively, nitrogen delivery was significantly lower in both groups on day 4 than the planned goal (0.10 versus 0.17 g of nitrogen/kg, $P < 0.05$). The mean volumes of enteral feeding for each of the first 5 postoperative days are shown in Fig. 1. Albumin concentrations between groups were equal before surgery, but albumin was depressed in the enriched group on day 6 compared with the standard nutrition group ($P < 0.05$; Table III). Transthyretin concentrations were decreased by 25% in both groups postoperatively ($P < 0.05$; Table III). Nitrogen balance was almost identical between groups (Fig. 2), and there were no significant differences in 3-methylhistidine excretion (Fig. 3).

Biochemical indicators of liver or renal function did not differ significantly between groups, and no differences were seen in electrolytes, platelet count, activated partial thromboplastin time, or prothrombin time (data not shown).

There were no significant differences in minor complications, length of stay in the hospital, or rate of readmission. Major complications requiring reoperation for intestinal obstruction occurred in one patient in the standard enteral group. No mortality occurred within 30 d after surgery.

DISCUSSION

Major abdominal surgery increases the risks of long-standing protein catabolism and compromised intestinal integrity. Enteral nutrition may improve clinical outcome in stress situations.^{1,3-5,7,13,14} Glutamine is considered a conditionally essential amino acid that could be described as a nutrient specific to the small bowel.⁶ AKG is the precursor to glutamine and therefore might be able to uphold glutamine levels during postoperative catabolism and attenuate muscle catabolism.^{9,10} In the current study, we found that AKG supplementation of a whole-protein-based enteral formula had no significant benefits on short-life plasma proteins, 3-methylhistidine excretion, nitrogen balance, or clinical outcome.

TABLE III.

SERUM ALBUMIN, TRANSTHYRETIN, UREA, AND C-PEPTIDE IN PATIENTS RECEIVING STANDARD ENTERAL NUTRITION OR α -KETOGUTARATE-SUPPLEMENTED ENTERAL NUTRITION FOR 5 DAYS AFTER MAJOR GASTROINTESTINAL SURGERY*

	Standard	Enriched
Albumin (g/L)		
Before surgery	40.0 (4.5)	38.3 (5.2)
Day 6 after surgery	37.4 (2.9)†	31.4 (4.4)†
Transthyretin (g/L)		
Before surgery	0.32 (0.03)	0.31 (0.03)
Day 6 after surgery	0.24 (0.02)†	0.23 (0.03)†
Urea (mM/L)		
Before surgery	5.3 (3.2)	5.1 (1.9)
Day 6 after surgery	8.1 (3.4)	6.6 (2.9)
C-peptide		
Before surgery	0.78 (0.24)	0.86 (0.10)
Day 6 after surgery	0.90 (0.10)	0.94 (0.26)

* Data presented as mean (standard error).

† $P < 0.05$ versus day 0.

‡ $P < 0.05$ versus the other nutritional group.

Interest in the role of glutamine in the catabolic state increased after parenteral glutamine and AKG were shown to have positive effects on muscle protein metabolism after cholecystectomy.⁹ Evidence from animal experiments suggested that glutamine is of vital importance to the intestine in different stressful situations.⁶ When studying the effects on human intestinal function, Van der

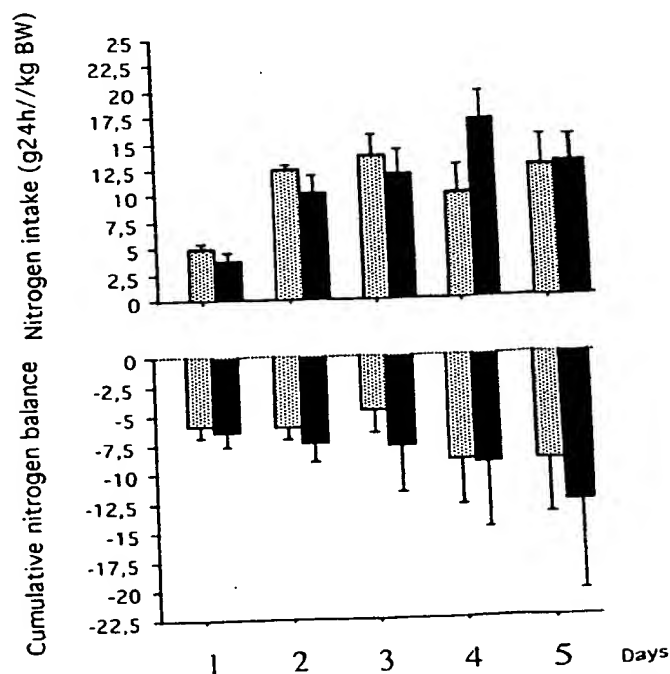


FIG. 2. Mean (standard error) nitrogen intake corrected for body weight (g/24 h per kilogram of body weight) and cumulative nitrogen balance (g/24 h) during 5 d postoperatively. Gray bars indicate standard nutrition, and black bars indicate AKG-supplemented nutrition. There were no significant differences between groups. AKG, α -ketoglutarate.

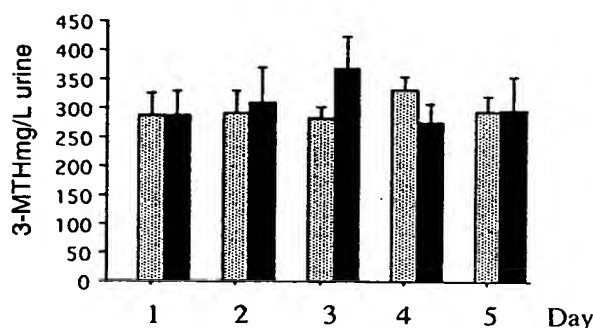


FIG. 3. Mean (standard error) urinary 3-methylhistidin excretion during 5 d postoperatively. Gray bars indicate standard nutrition, and black bars indicate AKG-supplemented nutrition. There were no significant differences between groups. AKG, α -ketoglutarate.

Hulst et al. developed data showing that parenteral glutamine attenuates the permeability disturbances that occur after gastrointestinal surgery.¹⁵ Other studies suggested that long-term mortality and the length of stay in the intensive care unit can be ameliorated by enteral glutamine.⁷ The beneficial effects of enteral glutamine were associated with an increase in plasma arginine, which could affect nitric oxide availability in immune-competent cells, that has not been seen with parenteral administration of glutamine.⁸

Several animal experiments showed that AKG in combination with ornithine (ornithine-ketoglutarate) spares glutamine in plasma, liver, and muscle and stimulates anabolic pathways (growth hormone and insulin).^{16–19} C-peptide was measured in the current study to determine whether AKG alone might influence insulin secretion. However, there were no differences in C-peptide release between groups receiving enriched or standard formula.

Postoperative parenteral administration of AKG was found to spare glutamine.¹⁰ We are not aware of any clinical studies using enteral AKG after surgery. In burned rats, enteral AKG in combination with ornithine or arginine caused a greater increase in plasma and muscle glutamine concentrations than did glycine.¹² In a animal model, we showed that the whole-protein-based formula that was used in this study stimulates ornithine-decarboxylase activity in the intestinal mucosa to a higher degree than any of the suggested gut nutrients (glutamine, ornithine-ketoglutarate, AKG, or arginine-ketoglutarate) in single administration.²⁰ Therefore, there may be additive effects on intestinal integrity by using a balanced whole-protein-based nutrition and a specific nutrient.

Because glutamine was present in the standard enteral formula we used, we wanted to combine it with an analog that did not increase the nitrogen load but was considered a gut nutrient and could be converted to glutamine and arginine. In humans, most AKG is metabolized in the mucosa.¹¹ However, long-term oral administration of AKG was shown to reduce urea and increase arginine concentrations in hemodialysis patients and, hence, to have general effects on protein metabolism.²¹ Plasma levels of amino acids were not analyzed in the present study. The increase in urea postoperatively was attenuated in the enriched group but not statistically different from the group receiving standard nutrition.

Adding AKG necessitated buffering the formula and increasing electrolyte content and, consequently, osmolality from 372 to 487 mOsm/L. However, it is unlikely that this change in osmolality had any substantial negative effect because we found no differences in the tolerance of the enteral feeding between groups of patients. The major problem in this study on early enteral feeding after major

surgery was the inability to reach the nutritional goal during the first 5 d after surgery. This difficulty might have obscured possible potential effects of the enrichment used. Despite differences being statistically non-significant, the longer operating time, larger blood loss, and higher frequency of upper gastrointestinal surgery in the study group also might have affected outcome.

In conclusion, we found no clinical or metabolic benefits when AKG was added to a whole-protein-based enteral formula administered via jejunostomy during the first 5 postoperative days in patients undergoing elective major abdominal surgery.

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(For an additional perspective, see Editorial Opinions)

APPENDIX C

No related proceedings are referenced in II. above, and hence copies of decisions in related proceedings are not provided.

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